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(71) Applicant *(for all designated States except US)*: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HALLETT, David, James [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). ROWLEY, Michael [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (US).

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(54) Title: INDOLE DERIVATIVES AS 5-HT2A RECEPTOR ANTAGONISTS

(57) Abstract

A class of 3-(piperidin-3-yl)-1*H*-indole derivatives and tetrahydropyridine analogues thereof bearing a range of substituents (including optionally substituted phenyl) at the 2-position of the indole ring system are selective antagonists of the human 5-HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including psychotic disorders such as schizophrenia.

INDOLE DERIVATIVES AS 5-HT2A RECEPTOR ANTAGONISTS

The present invention relates to a class of indole derivatives which act on serotonin receptors (also known as 5-hydroxytryptamine or 5-HT receptors). More particularly, the invention concerns 3-(piperidin-3-yl)-1*H*-indole derivatives which selective antagonists of the human 5-HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including psychotic disorders such as schizophrenia.

Schizophrenia is a disorder which is conventionally treated with drugs known as neuroleptics. In many cases, the symptoms of schizophrenia can be treated successfully with so-called "classical" neuroleptic agents such as haloperidol. Classical neuroleptics generally are antagonists at dopamine D_2 receptors.

Notwithstanding their beneficial antipsychotic effects, classical neuroleptic agents such as haloperidol are frequently responsible for eliciting acute extrapyramidal symptoms (movement disorders) and neuroendocrine (hormonal) disturbances. These side-effects, which plainly detract from the clinical desirability of classical neuroleptics, are believed to be attributable to D_2 receptor blockade in the striatal region of the brain.

The compound (+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)-ethyl]-4-piperidinemethanol (also known as MDL-100,907) is described in WO 91/18602. In preclinical studies, MDL-100,907 failed to induce catalepsy and failed to block apomorphine-induced stereotyped behaviour in animal models, strongly suggesting that this compound would be free from any liability to cause extrapyramidal side-effects. MDL-100,907 is currently undergoing clinical trials in schizophrenic patients and has demonstrated efficacy in a multicentre, placebo-controlled study for antipsychotic potential, with no neurological adverse effects. Pharmacologically, MDL-100,907 has been shown to be a potent

antagonist of human 5-HT_{2A} receptors, whilst being essentially devoid of activity at the human dopamine D_2 receptor. It is accordingly believed that compounds which can interact selectively with the 5-HT_{2A} receptor relative to the dopamine D_2 receptor will display the beneficial level of antipsychotic activity associated with 5-HT_{2A} receptor antagonism, whilst minimizing or even avoiding the extrapyramidal and other side-effects arising from an interaction with dopamine D_2 receptors.

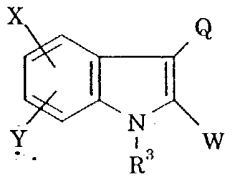
The compounds of the present invention are potent antagonists of the human 5-HT_{2A} receptor, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia. The compounds of the invention display more effective binding to the human 5-HT_{2A} receptor than to the human dopamine D_2 receptor, and they can therefore be expected to manifest fewer side-effects than compounds which do not discriminate in their binding affinity as between 5-HT_{2A} and D_2 receptors.

By virtue of their potent human 5-HT_{2A} receptor antagonist activity, the compounds of the present invention are also effective in the treatment of neurological conditions including depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, sleep disorders such as insomnia, eating disorders such as anorexia nervosa, and dependency or acute toxicity associated with narcotic agents such as LSD or MDMA; and cardiovascular conditions including variant angina, Raynaud's phenomenon, intermittent claudication, coronary and peripheral vasospasms, fibromyalgia, cardiac arrhythmias and thrombotic illness. They may also be generally of benefit in the inhibition of platelet aggregation, as well as in controlling the extrapyramidal symptoms associated with the administration of neuroleptic agents. They may further be effective in the lowering of intraocular pressure and may therefore be beneficial in treating glaucoma (cf. T. Mano *et al.* and H. Takaneka *et al.*, *Investigative Ophthalmology and Visual Science*, 1995, Vol. 36, pages 719 and 734 respectively).

Being 5-HT_{2A} receptor antagonists, the compounds of the present invention may also be beneficial in preventing or reducing the toxic symptoms associated with the intake of ergovaline in animals consuming *Acremonium coenophialum* infected tall fescue (cf. D. C. Dyer, *Life Sciences*, 1993, **53**, 223-228).

The compounds according to the present invention are potent and selective 5-HT_{2A} receptor antagonists having a human 5-HT_{2A} receptor binding affinity (K_i) of 100 nM or less, typically of 50 nM or less and preferably of 10 nM or less. The compounds of the invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT_{2A} receptor relative to the human dopamine D_2 receptor.

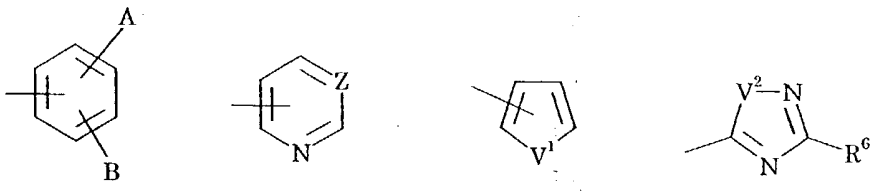
The present invention provides a compound of formula I, or a salt thereof:



(I)

wherein

W represents cyclohexyl, -CO_2R^4, -$CONHR^5$, or a group of formula (Wa), (Wb), (Wc) or (Wd):



(Wa) (Wb) (Wc) (Wd)

in which

Z represents CH or N;

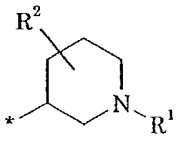
V^1 represents oxygen or sulphur;

V^2 represents oxygen or sulphur;

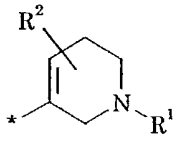
A and B independently represent hydrogen, hydroxy, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, hydroxymethyl or di(C_{1-6})alkylaminomethyl; or A and B, when situated on adjacent carbon atoms, together represent $-OCH_2O-$ or -CH=CH-CH=CH-;

X and Y independently represent hydrogen, halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy or phenyl;

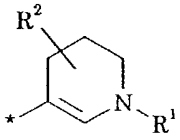
Q represents a group of formula (Qa), (Qb) or (Qc):



(Qa)



(Qb)



(Qc)

in which the asterisk denotes the point of attachment to the 3-position of the indole nucleus;

R^1 represents hydrogen, C_{1-6} alkyl, or an optionally substituted aryl(C_{1-6})alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl group;

R^2 represents hydrogen, hydroxy, halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

R^3 represents hydrogen or C_{1-6} alkyl;

R^4 represents C_{1-6} alkyl;

R^5 represents cyclohexyl, or a group of formula (Wa) as defined above; and

R^6 represents C_{1-6} alkyl, cyclohexyl, or a group of formula (Wa) as defined above.

The present invention also provides a compound of formula I as depicted above, or a salt thereof, wherein

W represents a group of formula (Wa) as depicted above, in which

A and B independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl or C_{1-6} alkoxy;

Q represents a group of formula (Qa), (Qb) or (Qc) as depicted above, in which

R^1 is as defined above; and

R^2 represents hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy; and

X, Y and R^3 are as defined above.

Where R^1 represents aryl(C_{1-6})alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl, this group may be optionally substituted by one or more substituents. Suitably, the group R^1 is unsubstituted, or substituted by one or two substituents. In general, the group R^1 may be unsubstituted or monosubstituted. Examples of optional substituents on the group R^1 include halogen, cyano, trifluoromethyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylaminomethyl, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, *N*-(C_{1-6})alkyl-*N*-(C_{2-6})alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, di(C_{1-6})alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl, di(C_{1-6})alkylaminosulphonyl, aminosulphonylmethyl, C_{1-6} alkylaminosulphonylmethyl and di(C_{1-6})alkylaminosulphonylmethyl.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl and *tert*-butyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio" and "C_{1-6} alkylamino" are to be construed accordingly.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl, especially phenylethyl.

Typical heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and imidazolidinonyl groups.

A particular C_{3-7} heterocycloalkyl(C_{1-6})alkyl group is imidazolidinonylethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Suitable values for the substituent A in the compounds of formula I above include hydrogen, hydroxy, fluoro, chloro, cyano, methyl, methoxy, isopropoxy, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl and dimethylaminomethyl. Particular values of A include hydrogen, fluoro, trifluoromethyl, methyl and methoxy, especially hydrogen or fluoro.

Suitably, B represents hydrogen, fluoro, chloro, cyano, nitro, trifluoromethyl, trifluoromethoxy, methyl or methoxy, especially hydrogen.

In addition, A and B, when attached to adjacent carbon atoms in the moiety (Wa), may together represent $-OCH_2O-$ or $-CH=CH-CH=CH-$.

Particular values for the substituent X include hydrogen, fluoro and methoxy, especially hydrogen.

Suitably, Y represents hydrogen, fluoro, chloro, bromo, methyl, methoxy or phenyl. Particular values of Y include hydrogen, fluoro, chloro and methyl, especially hydrogen.

In one embodiment, Z represents CH. In another embodiment, Z represents N.

In one embodiment, V^1 represents oxygen. In another embodiment, V^1 represents sulphur.

Suitably, V^2 represents oxygen.

Suitably, the moiety Q represents a group of formula (Qa) as defined above.

Suitably, R^1 represents hydrogen, methyl, benzyl, phenylethyl or imidazolidinonylethyl, especially hydrogen.

Suitably, R^2 represents hydrogen, hydroxy or halogen, especially hydrogen or halogen. Specific values of R^2 include hydrogen, hydroxy and fluoro. Particular values of R^2 include hydrogen and fluoro, especially fluoro.

Suitably, R^3 represents hydrogen or methyl, especially hydrogen.

Particular values of R^4 include methyl and ethyl, especially methyl.

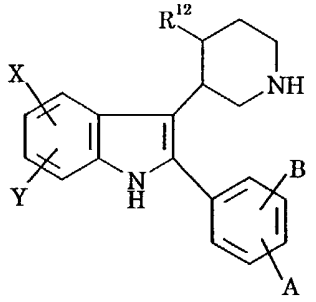
Particular values of R^5 include cyclohexyl, phenyl, chlorophenyl and ethoxycarbonyl-phenyl.

Suitably, R^6 represents methyl, cyclohexyl or phenyl, especially phenyl.

In one embodiment of the compounds of formula I in accordance with the present invention, the moiety W represents a group of formula (Wa) as defined above.

Specific values for the moiety W include cyclohexyl, methoxycarbonyl, cyclohexylaminocarbonyl, phenylaminocarbonyl, chlorophenyl-aminocarbonyl, ethoxycarbonylphenyl-aminocarbonyl, phenyl, hydroxyphenyl, fluorophenyl, cyanophenyl, methylphenyl, methoxyphenyl, isopropoxyphenyl, methoxycarbonyl-phenyl, hydroxymethyl-phenyl, dimethylaminomethyl-phenyl, methylenedioxy-phenyl, naphthyl, pyridinyl, pyrimidinyl, furyl, thienyl and phenyl-oxadiazolyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II, and salts thereof:



(II)

wherein

A, B, X and Y are as defined with reference to formula I above; and

R^{12} represents hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy.

Suitably, R^{12} represents hydrogen, fluoro, chloro, methyl or methoxy. Particular values of R^{12} include hydrogen and fluoro, especially fluoro.

Specific compounds within the scope of the present invention include:

3-(1-benzylpiperidin-3-yl)-2-phenyl-1*H*-indole;

3-(piperidin-3-yl)-2-phenyl-1*H*-indole;

3-[1-(2-phenylethyl)piperidin-3-yl]-2-phenyl-1*H*-indole;

3-(1-methylpiperidin-3-yl)-2-phenyl-1*H*-indole;

1-{2-[3-(2-phenyl-1*H*-indol-3-yl)piperidin-1-yl]ethyl}imidazolidin-2-one;

(3RS,4RS)-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

(+)-(3R,4R*)*-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

(+)-(3R,4R*)*-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

(3R,4R)-3-(4-fluoro-1-methylpiperidin-3-yl)-2-phenyl-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(furan-3-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid cyclohexylamide;

(3R,4R*)*-3-(2-phenyl-1*H*-indol-3-yl)piperidin-4-ol;

2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole;

6-fluoro-2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole;

6-fluoro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-fluoro-2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-chloro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-chloro-2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-fluoro-2-(2-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-chloro-2-(2-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

5-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

6-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

5-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

7-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

7-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

2-cyclohexyl-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-6-methyl-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-methoxyphenyl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-isopropoxyphenyl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(thien-2-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(thien-3-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(*m*-tolyl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(*o*-tolyl)-1*H*-indole;

(*3R*,4R**)-2-(benzo[1,3]dioxol-5-yl)-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyridin-3-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyridin-4-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyrimidin-5-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(naphthalen-1-yl)-1*H*-indole;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(naphthalen-2-yl)-1*H*-indole;

(*3R*,4R**)-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzonitrile;

(*3R*,4R**)-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]phenol;

(*3R*,4R**)-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzoic acid methyl ester;

(*3R*,4R**)-*N*-{3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzyl}-*N,N*-dimethylamine;

(*3R*,4R**)-{3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]phenyl}methanol;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid phenylamide;

(*3R*,4R**)-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid (4-chlorophenyl)amide;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid methyl ester;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-indole;

(3R,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-ylcarbonylamino]benzoic acid ethyl ester;

(3R,4R*)*-3-(6-fluoro-2-phenyl-1*H*-indol-3-yl)piperidin-4-ol;

and salts thereof.

The invention also provides pharmaceutical compositions comprising one or more of the compounds according to this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage

forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

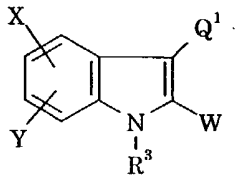
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

If desired, the compounds according to this invention may be co-administered with another anti-schizophrenic medicament, for example one producing its effects *via* dopamine D_2 and/or D_4 receptor subtype

blockade. In such circumstances, an enhanced anti-schizophrenic effect may be envisaged without a corresponding increase in side-effects such as those caused by, for example, D_2 receptor subtype blockade; or a comparable anti-schizophrenic effect with reduced side-effects may alternatively be envisaged. Such co-administration may be desirable where a patient is already established on an anti-schizophrenic treatment regime involving conventional anti-schizophrenic medicaments. Suitable anti-schizophrenic medicaments of use in combination with the compounds according to the present invention include haloperidol, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chloroprothixene, thiothixene, clozapine, olanzapine, pimozide, molindone, loxapine, sulpiride, risperidone, xanomeline, fananserin and ziprasidone, and pharmaceutically acceptable salts thereof.

The compounds according to the present invention wherein R^1 is other than hydrogen may be prepared by a process which comprises attachment of the R^1 moiety to a compound of formula III:



(III)

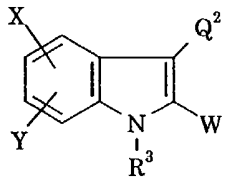
wherein W, X, Y and R^3 are as defined above, and Q^1 represents a group of formula (Qa), (Qb) or (Qc) as defined above in which R^1 is hydrogen; by conventional means including N-alkylation.

Attachment of the R^1 moiety to the compounds of formula III may conveniently be effected by standard alkylation techniques. One example thereof comprises treatment with an alkyl halide such as methyl iodide, an aryl(C_{1-6})alkyl halide such as benzyl bromide or 2-phenylethyl bromide, or a C_{3-7} heterocycloalkyl(C_{1-6})alkyl halide such as 2-(imidazolidin-2-on-1-

yl)ethyl chloride, typically under basic conditions, e.g. potassium carbonate or caesium carbonate in *N,N*-dimethylformamide. Another example comprises treatment of the compound of formula III with an aryl(C_{1-6})alkyl mesylate such as 2-phenylethyl methanesulphonate, typically in the presence of sodium carbonate and sodium iodide, in a suitable solvent such as 1,2-dimethoxyethane.

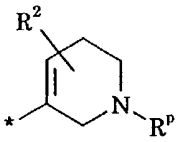
Alternatively, the R^1 moiety may conveniently be attached by reductive alkylation, which may be accomplished in a single step, or as a two-step procedure. The single-step approach suitably comprises treating the required compound of formula III as defined above with the appropriate aldehyde, e.g. formaldehyde, benzaldehyde or phenylacetaldehyde, in the presence of a reducing agent such as sodium cyanoborohydride. In a typical two-step procedure, for the preparation of a compound of formula I wherein R^1 corresponds to a group of formula $-CH_2R^{1a}$, a carboxylic acid derivative of formula R^{1a}-CO_2H is condensed with the required compound of formula III, suitably in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, to afford a compound corresponding to formula I wherein R^1 represents $-COR^{1a}$; the carbonyl group thereof can then be reduced, for example by treatment with diisobutylaluminium hydride, and the required compound of formula I thereby obtained.

The compounds of formula III above wherein Q^1 represents a group of formula (Qa) in which R^1 is hydrogen may be prepared by reduction of the corresponding compound of formula IV:

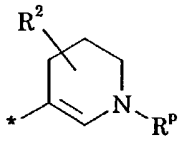


(IV)

wherein W, X, Y and R^3 are as defined above, and Q^2 represents a group of formula (Qd) or (Qe), or a mixture thereof:



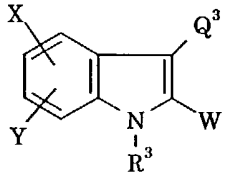
(Qd)



(Qe)

in which the asterisk denotes the point of attachment to the 3-position of the indole nucleus, R^2 is as defined above, and R^P represents an amino-protecting group; followed by removal of the amino-protecting group R^P.

Similarly, the compounds according to the invention wherein Q represents a group of formula (Qa) as defined above may be prepared by a process which comprises reducing a compound of formula V:



(V)

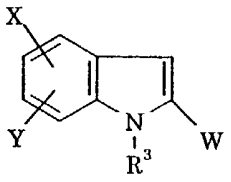
wherein W, X, Y and R^3 are as defined above, and Q^3 represents a group of formula (Qb) or (Qc) as defined above, or a mixture thereof.

Reduction of the compounds of formula IV or V may conveniently be accomplished by conventional catalytic hydrogenation, which comprises treating the appropriate compound with hydrogen in the presence of a hydrogenation catalyst such as palladium on charcoal. Alternatively, compound IV or V may be reduced by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a

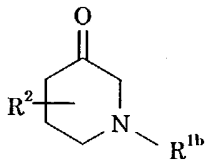
hydrogen donor such as ammonium formate, typically in a lower alkanol solvent such as methanol.

The amino-protecting group R^p in the compounds of formula IV is suitably benzyl, in which case the amino-protecting group R^p can conveniently be removed as necessary by transfer hydrogenation utilising the conditions described above. Alternatively, the amino-protecting group R^p may be a carbamoyl moiety such as benzyloxycarbonyl, which can conveniently be removed as necessary by treatment with a hydrogenation catalyst such as palladium on charcoal, typically in methanol/formic acid.

The intermediates of formula IV and V may be prepared by reacting a compound of formula VI with the appropriate piperidinone derivative of formula VII:



(VI)

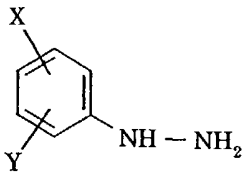


(VII)

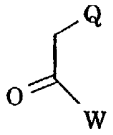
wherein W, X, Y, R^2 and R^3 are as defined above, and R^{1b} represents an amino-protecting group R^p as defined above or corresponds to the moiety R^1 as defined above.

The reaction between compounds VI and VII is conveniently effected by heating the reactants under acidic conditions, typically in a mixture of phosphoric acid and acetic acid at a temperature in the region of 80°C.

In another procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula VIII or an acid addition salt thereof, typically the hydrochloride salt, with a compound of formula IX:



(VIII)

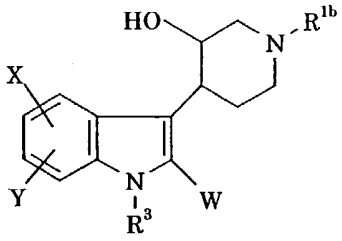


(IX)

wherein W, X, Y and Q are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

The reaction between compounds VIII and IX, which is an example of the well-known Fischer indole synthesis, is suitably effected by stirring in ethanol at 25°C, followed by heating in trifluoroacetic acid at 70°C.

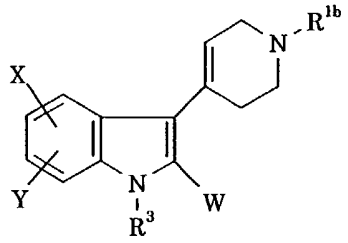
The compounds according to the invention wherein Q represents a group of formula (Qa) as defined above and R^2 represents fluoro in the 4-position of the piperidine ring may be prepared by a process which comprises treating a compound of formula X:



(X)

wherein W, X, Y, R^{1b} and R^3 are as defined above; with diethylamino-sulphur trifluoride (DAST); followed, where necessary, by removal of the amino-protecting group R^P.

The compounds of formula X above may be prepared from the corresponding compound of formula XI:

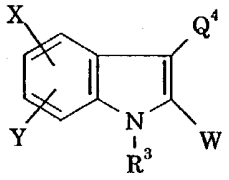


(XI)

wherein W, X, Y, R^{1b} and R^3 are as defined above; by hydroboration followed by oxidation.

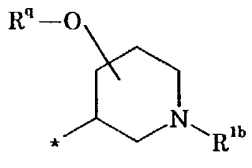
The compounds of formula XI may be prepared by methods analogous to those described above for the preparation of compounds IV and V.

The compounds according to the invention wherein R^2 represents hydroxy may be prepared by a process which comprises removing the hydroxy-protecting group from a compound of formula XII:

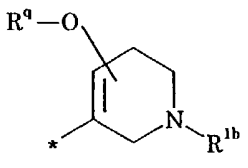


(XII)

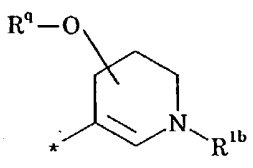
wherein W, X, Y and R^3 are as defined above, and Q^4 represents a group of formula (Qf), (Qg) or (Qh):



(Qf)



(Qg)

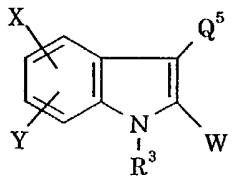


(Qh)

in which the asterisk denotes the point of attachment to the 3-position of the indole nucleus, R^{1b} is as defined above, and R^q represents a hydroxy-protecting group; followed, where necessary, by removal of the amino-protecting group R^p.

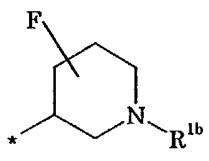
The hydroxy-protecting group R^q in the compounds of formula XII is suitably 4-nitrobenzoyl, in which case it can conveniently be removed as necessary by treatment with a base such as potassium carbonate in an appropriate solvent, typically a lower alkanol such as methanol.

The intermediates of formula XII above may be prepared by reacting a compound of formula R^q-OH with a compound of formula XIII:

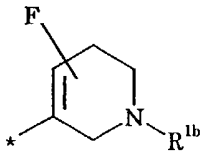


(XIII)

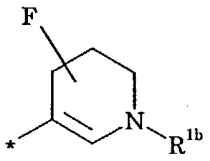
wherein W, X, Y, R^3 and R^q are as defined above, and Q^5 represents a group of formula (Qi), (Qj) or (Qk):



(Qi)



(Qj)



(Qk)

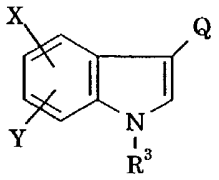
wherein the asterisk denotes the point of attachment to the 3-position of the indole nucleus, and R^{1b} is as defined above.

By way of illustration, where R^q represents 4-nitrobenzoyl the reaction between compound XIII and the compound of formula R^q-OH may

conveniently be effected by stirring the reactants in a solvent such as tetrahydrofuran, in the presence of triphenylphosphine and diethyl azodicarboxylate.

In an illustrative procedure, certain compounds of formula XIII above may be prepared by treatment of the appropriate precursor of formula X as defined above with DAST.

The compounds according to the invention wherein W represents cyclohexyl or a group of formula (Wa), (Wb), (Wc) or (Wd) may be prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:



(XIV)

W^1— L^1

(XV)

wherein X, Y, Q and R^3 are as defined above, W^1 represents cyclohexyl or a group of formula (Wa), (Wb), (Wc) or (Wd) as defined above, and L^1 represents a suitable leaving group; in the presence of a transition metal catalyst.

The leaving group L^1 is suitably a halogen atom, e.g. bromo.

A suitable transition metal catalyst for use in the reaction between compounds XIV and XV is tetrakis(triphenylphosphine)palladium(0), in which case the reaction is conveniently effected under basic conditions, e.g. in the presence of the anion derived from 2,2,6,6-tetramethylpiperidine.

The compounds according to the invention wherein W represents -CONHR^5 may be prepared by a process which comprises reacting a compound of formula XIV as defined above with a compound of formula R^5-N=C=O wherein R^5 is as defined above; in the presence of a transition metal catalyst; with subsequent acidification.

A suitable transition metal catalyst of use in this reaction is tetrakis(triphenylphosphine)palladium(0), in which case the reaction is conveniently effected under basic conditions, e.g. in the presence of the anion derived from 2,2,6,6-tetramethylpiperidine. The resulting product is then acidified *in situ*, typically by the addition of glacial acetic acid.

Where they are not commercially available, the starting materials of formula VI, VII, VIII, IX, XIV and XV may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. Indeed, as will be appreciated, the compounds of formula III and V above, the compounds of formula XIII wherein R^{1b} corresponds to a moiety of formula R^1, and the compounds of formula IV and XIII wherein the amino-protecting group R^p is, for example, benzyl, are compounds according to the invention in their own right.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds of use in the invention.

The compounds in accordance with this invention potently inhibit [^{3}H]-ketanserin binding to the human 5-HT_{2A} receptor expressed in clonal cell lines. Moreover, those compounds of the invention which have been tested display a selective affinity for the 5-HT_{2A} receptor relative to the dopamine D_2 receptor.

The compounds of the accompanying Examples were all found to possess a K_i value for displacement of [^{3}H]-ketanserin from the human 5-HT_{2A} receptor, when expressed in Chinese hamster ovary (CHO) clonal cell lines, of 100 nM or less.

EXAMPLE 1

3-(1-Benzylpiperidin-3-yl)-2-phenyl-1*H*-indole

2-Phenylindole (2 g, 10.4 mmol) was stirred at 80°C in AcOH (20 ml), and 1-benzyl-3-piperidone hydrochloride hydrate (5 g, 21.4 mmol) and 1M phosphoric acid (10 ml) added. After a further 4 h, the mixture was poured into ice/ammonia, and extracted with EtOAc (2 x 20 ml). The combined organic layers were washed with water and brine, dried, and evaporated *in vacuo* and purified by flash chromatography, eluting with dichloromethane:methanol:880 ammonia (97:3:0.3 v/v) to give a pale yellow oil (6 g). This was a mixture of the two isomeric tetrahydropyridine

products which were unstable, and starting benzylpiperidone. The oil was hydrogenated on Pd/C (10% w/w, 0.6 g) in ethanol (50 ml) and conc. HCl (3 ml) at 50 psi overnight. The mixture was filtered, poured into saturated $NaHCO_3$, and extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with water and brine, dried, and evaporated *in vacuo* and purified by flash chromatography, eluting with dichloromethane: methanol:880 ammonia (98.5:1.5:0.15 v/v) to give a white solid (2.2 g, 58%), oxalate salt mp 267-270°C (from EtOH) (Found C, 76.59; H, 6.70; N, 6.43. $C_{26}H_{26}N_2$. 0.7 $C_2H_2O_4$ requires C, 76.62; H, 6.43; N, 6.52%); δ_H (360 MHz, d_6-DMSO) 1.6-1.7 (1H, m, piperidine H), 1.8-1.9 (2H, m, piperidine H), 2.0-2.1 (1H, m, piperidine H), 2.6-2.7 (1H, m, piperidine H), 3.0-3.1 (3H, m, piperidine H), 3.2-3.3 (1H, m, piperidine H), 3.95 (2H, br s, $PhCH_2$), 7.00 (1H, t, *J* 7, indole-H), 7.09 (1H, t, *J* 7, indole-H), 7.2-7.6 (11H, m, ArH), 7.80 (1H, d, *J* 7, ArH), 11.2 (1H, br s, indole NH); *m/z* (ES^+) 367 (M^++H).

EXAMPLE 2

3-(Piperidin-3-yl)-2-phenyl-1*H*-indole

3-(1-Benzylpiperidin-3-yl)-2-phenyl-1*H*-indole (2.1 g, 5.7 mmol), palladium on carbon (10% w/w, 0.21 g) and ammonium formate (2.3 g, 29 mmol) were refluxed in MeOH (30 ml) for 24 h. The mixture was cooled, filtered, and purified by flash chromatography, eluting with dichloromethane:methanol:880 ammonia (98.5:1.5:0.15 v/v) to give a white solid (1.1 g, 50%); oxalate salt, white crystals, mp 258-262°C (from EtOH) (Found C, 70.53; H, 6.84; N, 7.85. $C_{19}H_{20}N_2$. 0.5 $C_2H_2O_4$. H_2O requires C, 70.77; H, 6.83; N, 8.25%); δ_H (400 MHz, d_6-DMSO) 1.6-1.8 (1H, m, piperidine H), 1.8-1.9 (2H, m, piperidine H), 2.2-2.4 (1H, m, piperidine H), 3.00 (1H, t, *J* 12, piperidine H), 3.2-3.5 (4H, m, piperidine H), 6.98 (1H, t, *J* 7, indole-H), 7.09 (1H, t, *J* 7, indole-H), 7.2-7.5 (6H, m, ArH), 7.84 (1H, d, *J* 8, ArH), 11.3 (1H, br s, indole NH); *m/z* (ES^+) 277 (M^++H).

EXAMPLE 3

3-[1-(2-Phenylethyl)piperidin-3-yl]-2-phenyl-1*H*-indole

3-(Piperidin-3-yl)-2-phenyl-1*H*-indole (210 mg, 0.76 mmol), phenethyl bromide (140 µl, 1 mmol), and Cs_2CO_3 (0.35 g, 1 mmol) were stirred in DMF (3 ml) at 60°C overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried, and evaporated *in vacuo* and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (97:3:0.3 v/v) to give the product (251 mg, 87%) as a colourless oil: oxalate salt, white crystals, mp 142-145°C (from Et_2O) (Found C, 71.88; H, 6.94; N, 5.53. $C_{27}H_{28}N_2$. $C_2H_2O_4$. 0.8 H_2O requires C, 71.82; H, 6.57; N, 5.78%); δ_H (360 MHz, d_6-DMSO) 1.8-1.9 (2H, m, piperidine H), 1.9-2.0 (1H, m, piperidine H), 2.2-2.3 (1H, m, piperidine H), 2.9-3.0 (2H, m, CH_2), 3.02 (1H, t, *J* 12, piperidine H), 3.2-3.3 (2H, m, CH_2), 3.4-3.5 (4H, m, piperidine H), 7.00 (1H, t, *J* 7, indole-H), 7.11 (1H, t, *J* 7, indole-H), 7.2-7.6 (11H, m, ArH), 7.89 (1H, d, *J* 8, ArH), 11.3 (1H, br s, indole NH); *m/z* (ES^+) 381 (M^++H).

EXAMPLE 4

3-(1-Methylpiperidin-3-yl)-2-phenyl-1*H*-indole

3-(Piperidin-3-yl)-2-phenyl-1*H*-indole (200 mg, 0.7 mmol), sodium cyanoborohydride (51 mg, 0.8 mmol), formaldehyde (60 µl, 40% in H_2O, 0.8 mmol) and AcOH (97 µl, 1.7 mmol) were stirred in MeOH (5 ml) at 0°C for 1 h, then room temperature for 2 h. The solution was poured into saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with water and brine, dried, evaporated *in vacuo*, and purified by preparative thin layer chromatography, eluting with CH_2Cl_2:MeOH: 880 ammonia (97:3:0.3 v/v) to give the product (172 mg, 82%) as a colourless oil; oxalate salt, mp 287-290°C (from EtOH) (Found C, 72.69; H,

7.07; N, 8.01. $C_{20}H_{22}N_2$. 0.5 $C_2H_2O_4$. 0.7 H_2O requires C, 72.47; H, 7.07; N, 8.05%); δ_H (360 MHz, d_6-DMSO) 1.7-1.8 (1H, m, piperidine H), 1.8-1.9 (2H, m, piperidine H), 2.0-2.1 (1H, m, piperidine H), 2.5 (3H, s, Me), 2.6-2.7 (1H, m, piperidine H), 3.0-3.2 (3H, m, piperidine H), 3.2-3.3 (1H, m, piperidine H), 6.99 (1H, t, *J* 7, indole-H), 7.09 (1H, t, *J* 7, indole-H), 7.2-7.5 (6H, m, ArH), 7.82 (1H, d, *J* 8, ArH), 11.2 (1H, br s, indole NH); *m/z* (ES^+) 291 (M^++H).

EXAMPLE 5

1-{2-[3-(2-Phenyl-1*H*-indol-3-yl)piperidin-1-yl]ethyl}imidazolidin-2-one

3-(Piperidin-3-yl)-2-phenyl-1*H*-indole (172 mg, 0.62 mmol), 1-(2-chloroethyl)imidazolidin-2-one (119 mg, 0.80 mmol), and Cs_2CO_3 (0.29 g, 0.8 mmol) were stirred in DMF (3 ml) at 70°C for 6 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried, and evaporated *in vacuo* and purified by flash chromatography eluting with CH_2Cl_2:MeOH:880 ammonia (97:3:0.3 v/v) to give the product (201 mg, 83%) as a colourless oil: oxalate salt, white crystals, mp 203-205°C (from EtOH) (Found C, 71.88; H, 6.94; N, 5.53. $C_{27}H_{28}N_2$. $C_2H_2O_4$. 0.8 H_2O requires C, 71.82; H, 6.57; N, 5.78%); δ_H (360 MHz, d_6-DMSO) 1.7-1.8 (1H, m, piperidine H), 1.8-1.9 (2H, m, piperidine H), 1.9-2.0 (1H, m, piperidine H), 2.2-2.3 (1H, m, piperidine H), 2.7-3.4 (13H, m, CH and CH_2), 6.4 (1H, s, NH), 7.00 (1H, t, *J* 7, indole-H), 7.09 (1H, t, *J* 7, indole-H), 7.2-7.6 (11H, m, ArH), 7.83 (1H, d, *J* 8, ArH), 11.2 (1H, br s, indole NH); *m/z* (ES^+) 389 (M^++H).

EXAMPLE 6

(3RS,4RS)-3-(4-Fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

2-Phenylindole (25 g, 130 mmol) was stirred at 80°C in AcOH (200 ml), and 4-piperidone hydrochloride hydrate (50 g, 376 mmol) and 1M

phosphoric acid (100 ml) added. After a further 6 h, the mixture was poured into ice/ammonia, and extracted with EtOAc (3 x 200 ml). The combined organic layers were washed with water and brine, dried, and evaporated *in vacuo* to give a pale yellow solid. This was suspended in boiling EtOAc (200 ml), cooled to room temperature overnight, and the solid collected, washed with EtOAc and dried to give the 3-(1,2,3,6-tetrahydropyridin-4-yl)-2-phenyl-1*H*-indole (26 g, 73%) as a pale yellow solid; δ_H (360 MHz, d_6-DMSO) 2.0-2.1 (2H, m, NCH_2CH_2), 2.89 (2H, t, *J* 5, NCH_2CH_2), 3.40-3.45 (2H, m, NCH_2CH), 5.78 (1H, br s, NCH_2CH), 7.00 (1H, t, *J* 7, indole-H), 7.08 (1H, t, *J* 7, indole-H), 7.2-7.5 (5H, m, ArH), 7.69 (2H, d, *J* 7, ArH), 11.3 (1H, br s, indole NH); *m/z* (ES^+) 275 (M^++H).

A solution of 3-(1,2,3,6-tetrahydropyridin-4-yl)-2-phenyl-1*H*-indole (10.0 g, 36.5 mmol) in chloroform (175 ml) was treated with solid potassium carbonate (7.5 g, 54.3 mmol) and then with benzyl chloroformate (5.9 ml, 41.3 mmol). The resulting suspension was heated at reflux for 14 hours, cooled to ambient temperature and treated with *N,N*-diethylethylenediamine (1.5 ml, 10.7 mmol). After stirring at ambient temperature for 1 hour the majority of the solvent was removed *in vacuo* and the resulting residue partitioned between ethyl acetate (500 ml) and water (500 ml). The organic phase was then washed with 0.1N hydrochloric acid (2 x 500 ml), water (500 ml), brine (500 ml) and dried over anhydrous sodium sulfate. Filtration and evaporation to dryness furnished the 4-(2-phenyl-1*H*-indol-3-yl)-2,3-dihydro-6*H*-pyridine-1-carboxylic acid benzyl ester (14.9 g, 100%) as a pale orange foam: δ_H (360 MHz, $CDCl_3$) 2.20-2.40 (2H, m, NCH_2CH_2), 3.66 (2H, t, *J* 5.5, NCH_2CH_2), 4.18-4.24 (2H, m, NCH_2CH), 5.19 (2H, s, CH_2O), 5.80-5.95 (1H, m, NCH_2CH), 7.16 (1H, t, *J* 7, indole-H), 7.21 (1H, dt, *J* 7, and 1, indole-H), 7.23-7.41 (9H, m, ArH), 7.56 (2H, d, *J* 7, ArH), 7.63 (1H, d, *J* 8, ArH), 8.17 (1H, s, indole NH); *m/z* (ES^+) 409 (M^++H).

A cooled (-25°C) solution of 4-(2-phenyl-1*H*-indol-3-yl)-2,3-dihydro-6*H*-pyridine-1-carboxylic acid benzyl ester (2.6 g, 6.4 mmol) in anhydrous

tetrahydrofuran (50 ml) was treated with borane-methyl sulfide complex (650 ml of a 10 molar solution, 6.5 mmol) and this mixture was stirred with warming to ambient temperature over 16 hours. The reaction was then cooled to -10°C and treated with 3N sodium hydroxide solution (2 ml) followed by hydrogen peroxide (1 ml of a 30 wt. % solution in water) and this mixture was stirred with warming to ambient temperature over 24 hours. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate (250 ml) and extracted with ethyl acetate (2 x 150 ml). The organics were combined, washed with water (250 ml), brine (250 ml) and dried over anhydrous sodium sulfate. Filtration and evaporation to dryness gave the (*3RS,4RS*)-3-hydroxy-4-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (2.7 g, 100%) as a white foam which was used without further purification. A small sample was recrystallised from diethyl ether giving white needles, mp 147-149°C: δ_H (360 MHz, $CDCl_3$) 1.76-1.86 (2H, m, piperidine 5-H and OH), 2.20-2.40 (1H, m, piperidine 5-H), 2.62-2.86 (2H, m, piperidine 2-H and piperidine 6-H), 3.00-3.10 (1H, m, piperidine 4-H), 4.18-4.38 (2H, m, piperidine-H), 4.50-4.64 (1H, m, piperidine-H), 5.20 (2H, s, CH_2O), 7.11 (1H, dt, *J* 8 and 1, indole-H), 7.23 (1H, dt, *J* 7 and 1, indole-H), 7.35-7.48 (9H, m, ArH), 7.60 (2H, d, *J* 7, ArH), 7.68 (1H, d, *J* 8, ArH), 8.15 (1H, s, indole NH); *m/z* (ES^+) 427 (M^++H).

A cooled (-50°C) solution of (*3RS,4RS*)-3-hydroxy-4-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (1.0 g, 2.3 mmol) in anhydrous ethyl acetate (20 ml) was treated with diethylaminosulfur trifluoride (350 ml, 2.6 mmol). Stirring at -50°C was continued for 1 hour before allowing the solution to warm to ambient temperature over 3 hours. The reaction mixture was then poured into saturated aqueous sodium hydrogen carbonate (100 ml) and the product extracted into ethyl acetate (100 ml). The organic phase was washed with water (100 ml), brine (100 ml), then dried over anhydrous sodium sulfate. This solution was filtered, treated with decolourising charcoal (0.5 g) and filtered again. The

resulting pale yellow filtrate was then treated with Raney® nickel (1 ml of a 50% slurry in water). After standing at ambient temperature for 2 hours the solution was filtered and evaporated to dryness to afford the (*3RS,4RS*)-4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (1.0 g, 100%) as a pale yellow solid which was used without further purification. A small sample was recrystallised from ethanol giving white needles, mp 199-201°C: δ_H (360 MHz, $CDCl_3$) 1.70-1.85 (1H, m, piperidine-H), 2.20-2.30 (1H, m, piperidine-H), 2.90-3.10 (1H, m, piperidine-H), 3.20-3.30 (1H, m, piperidine-H), 3.40-3.50 (1H, m, piperidine-H), 4.20-4.50 (2H, m, piperidine-H), 5.10 (2H, s, CH_2O), 5.24 (1H, dtd, *J* 54, 11 and 5, piperidine 4-H), 7.12 (1H, t, *J* 7, indole-H), 7.18 (1H, t, *J* 7, indole-H), 7.20-7.43 (9H, m, ArH), 7.52-7.56 (2H, m, ArH), 7.67 (1H, d, *J* 8, ArH), 8.15 (1H, s, indole NH); *m/z* (ES^+) 429 (M^++H).

A solution of (*3RS,4RS*)-4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic acid benzyl ester (975 mg, 2.3 mmol) in ethyl acetate (50 ml) was treated with 99% formic acid (5 ml) and then with 10% palladium on activated carbon (120 mg) and the resulting suspension stirred at ambient temperature for 4 hours. The reaction mixture was filtered and pre-adsorbed directly on to silica gel. Purification on the same eluting with dichloromethane/methanol/880 ammonia (93:7:1) followed by recrystallisation from methanol gave the *title compound* (600 mg, 90%) as white needles, mp 134-136°C (Found C, 73.66; H, 7.05; N, 8.62. $C_{19}H_{19}FN_2.CH_4O$ requires C, 73.59; H, 7.10; N, 8.58%); δ_H (360 MHz, d_6-DMSO) 1.42-1.58 (1H, m, piperidine 5-H), 2.08-2.18 (1H, m, piperidine 5-H), 2.72 (1H, t, *J* 12.5, piperidine 6-H), 2.90-2.98 (1H, m, piperidine 2-H), 3.00-3.18 (3H, m, piperidine 2-H, 3-H and 6-H), 4.02-4.15 (1H, br, piperidine NH), 5.20 (1H, dtd, *J* 54, 11 and 5, piperidine 4-H), 6.99 (1H, t, *J* 7, indole-H), 7.10 (1H, t, *J* 7, indole-H), 7.36-7.42 (2H, m, ArH), 7.52 (2H, t, *J* 8, ArH), 7.58 (2H, d, *J* 8, ArH), 7.76 (1H, d, *J* 8, ArH), 11.21 (1H, s, indole NH); *m/z* (ES^+) 295 (M^++H).

EXAMPLE 7

(+)-(3R,4R*)*-3-(4-Fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

A cooled (-10°C) suspension of (-)-diisopinocampheylborane (9.8 g, 34.2 mmol, prepared from (1*R*)-(+)-α-pinene (>91% e.e.) according to H. C. Brown and B. Singaram, *J. Org. Chem.*, 1984, *49*, 945-947) in anhydrous tetrahydrofuran (30 ml) was treated with a solution of 4-(2-phenyl-1*H*-indol-3-yl)-2,3-dihydro-6*H*-pyridine-1-carboxylic acid benzyl ester (7.0 g, 17.1 mmol) in anhydrous tetrahydrofuran (40 ml) and this mixture was stirred to ambient temperature over 40 hours. The reaction was then cooled to -10°C and treated with 4N sodium hydroxide solution (20 ml) followed by hydrogen peroxide (12 ml of a 30 wt. % solution in water) and this mixture was stirred to ambient temperature over 24 hours. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate (500 ml) and extracted with ethyl acetate (2 x 250 ml). The organics were combined, washed with water (400 ml), brine (400 ml), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give a yellow oil. Purification by chromatography on silica gel eluting with hexanes on a gradient up to 40% ethyl acetate gave the title compound (6.4 g, 88%) as a white solid (50% e.e. by HPLC). Recrystallisation from diethyl ether over 5 days gave white needles and a mother liquor enriched in the major enantiomer. Filtration followed by concentration of the filtrate *in vacuo* gave *(3R*,4R*)*-3-hydroxy-4-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester as a pale yellow foam (4.4 g, 79% e.e. by HPLC). Spectroscopic data as for racemate. HPLC examination of the crystalline material (2.2 g) showed it to be racemic.

(3R,4R*)*-3-Hydroxy-4-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (4.4 g, 10.3 mmol, 79% e.e.) and diethylaminosulfur trifluoride (1.8 ml, 13.6 mmol) gave *(3R*,4R*)*-4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester as a pale yellow foam (4.4 g, 100%). Spectroscopic data as for racemate.

The title compound was prepared as described in Example 6 above using *(3R*,4R*)*-4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (4.4 g, 10.3 mmol) affording a white solid (2.1 g, 70%). Two recrystallisations from methanol gave the *title compound* (1.2 g) as white needles, mp 124-126°C (Found C, 74.12; H, 6.94; N, 8.53. $C_{19}H_{19}FN_2$. 0.9 CH_4O requires C, 73.95; H, 7.05; N, 8.67%); >99% e.e. (HPLC); $[\alpha]_D$ +20.2 (c 1.5 in DMF). Other data as for racemate.

EXAMPLE 8

(+)-(3R,4R*)*-2-(4-Fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

2-(4-Fluorophenyl)-1*H*-indole (6.00 g, 28.4 mmol) was stirred at 90°C in AcOH (60 ml), and 4-piperidone hydrochloride hydrate (8.00 g, 51.3 mmol) and 1M phosphoric acid (15 ml) added. After a further 60 h, the mixture was poured into ice/ammonia. EtOAc (300 ml) was added and the mixture stirred for 45 mins. The layers were separated and the aqueous layer extracted with EtOAc (3 x 200 ml). The combined organic layers were washed with water (250 ml), brine (250 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give a brown solid. This was stirred with Et_2O (200 ml) for 4 h. The mixture was filtered affording 2-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole as a tan solid (7.12 g, 86%); δ_H (360 MHz, d_6-DMSO) 2.08-2.10 (2H, m, NCH_2CH_2), 2.90 (2H, t, *J* 6, NCH_2CH_2), 3.39-3.41 (2H, m, NCH_2CH), 5.79 (1H, br s, NCH_2CH), 7.01 (1H, t, *J* 7, indole-H), 7.13 (1H, t, *J* 7, indole-H), 7.3-7.4 (3H, m, 2 ArH + indole-H), 7.50 (1H, d, *J* 8, indole-H), 7.71 (2H, dd, *J* 7 and 3, ArH), 11.3 (1H, br s, indole NH); *m/z* (ES^+) 293 (M^++H).

A solution of 2-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (5.64 g, 19.32 mmol) in chloroform (100 ml) was treated with solid potassium carbonate (3.70 g, 26.8 mmol) and then with benzyl chloroformate (3.3 ml, 23.1 mmol). The resulting suspension was heated at 50°C for 14 hours, cooled to ambient temperature and treated with *N,N*-

diethylethylenediamine (1.5 ml, 10.7 mmol). After stirring at ambient temperature for 1 hour the majority of the solvent was removed *in vacuo* and the resulting residue partitioned between ethyl acetate (300 ml) and water (300 ml). The organic phase was then washed with 1N citric acid (2 x 200 ml), water (300 ml), brine (200 ml) and dried ($MgSO_4$). The crude product was purified by flash chromatography (20% EtOAc/hexane) to furnish 4-[2-(4-fluorophenyl)-1*H*-indol-3-yl]-2,3-dihydro-6*H*-pyridine-1-carboxylic acid benzyl ester (8.14 g, 99%) as a pale orange foam: δ_H (360 MHz, DMSO) 2.20-2.30 (2H, m, NCH_2CH_2), 3.55-3.70 (2H, m, NCH_2CH_2), 4.09-4.20 (2H, m, NCH_2CH), 5.14 (2H, s, CH_2O), 5.77-5.83 (1H, m, NCH_2CH), 7.01 (1H, t, *J* 7, indole-H), 7.10 (1H, t, *J* 7, indole-H), 7.27-7.44 (7H, m, ArH), 7.52 (1H, d, *J* 8, indole-H), 7.66 (2H, dd, *J* 9 and 6, ArH), 11.40 (1H, br s, indole NH); *m/z* (ES^+) 427 (M^++H).

A solution of 4-[2-(4-fluorophenyl)-1*H*-indol-3-yl]-2,3-dihydro-6*H*-pyridine-1-carboxylic acid benzyl ester (8.14 g, 19.1 mmol) in anhydrous tetrahydrofuran (100 ml) was added *via* cannula to a suspension of diisopinocampheylborane derived from (*R*)-pinene (9.79 g, 34.2 mmol) in anhydrous THF (20 ml). The mixture was stirred at ambient temperature for 62 hours. The reaction was then cooled to 0°C and treated with 3N sodium hydroxide solution (20 ml) followed by hydrogen peroxide (20 ml of a 30 wt. % solution in water) and this mixture was stirred with warming to ambient temperature over 16 hours. A further portion of hydrogen peroxide (10 ml of a 30 wt. % solution in water) was added and the reaction stirred for 4 h. The layers were separated and the aqueous layer extracted with EtOAc (3 x 50 ml). The combined organic fractions were washed with H_2O (100 ml), brine (100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product purified by flash chromatography (15-40% EtOAc/hexane) to afford (*3R*,4R**)-3-hydroxy-4-[2-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic acid benzyl ester (6.91 g, 81%) as a yellow foam which was used without further purification. Chiral HPLC analysis indicated an enantiomeric excess of

81%: δ_H (360 MHz, $CDCl_3$) 1.70-1.86 (2H, m, piperidine 5-H), 2.20-2.40 (1H, m, piperidine 4-H), 2.62-2.83 (2H, m, piperidine 2-H and piperidine 6-H), 2.96 (1H, td, *J* 13 and 4, piperidine 4-H), 4.15-4.23 (2H, m, piperidine 2-H and piperidine 6-H), 4.55 (1H, br s, OH), 5.19 (2H, s, CH_2O), 7.09-7.25 (4H, m, ArH), 7.33-7.40 (6H, m, ArH), 7.58 (2H, dd, *J* 8 and 5, ArH), 7.66 (1H, d, *J* 8, indole-H), 8.15 (1H, s, indole NH); *m/z* (ES^+) 445 (M^++H).

A cold (-78°C), stirred solution of (*3R*,4R**)-3-hydroxy-4-[2-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic acid benzyl ester (2.34 g, 5.25 mmol) in anhydrous ethyl acetate (100 ml) was treated with diethylaminosulfur trifluoride (840 ml, 6.83 mmol). The reaction was stirred at -78°C for 1 h before removal from the cold bath and subsequent stirring for 45 mins. Saturated aqueous sodium hydrogen carbonate (50 ml) was added and the layers separated, the aqueous layer was extracted with ethyl acetate (3 x 50 ml). The organic phase was washed with water (50 ml), brine (75 ml) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude reaction mixture eluted through a short column of silica gel (20% EtOAc/hexane). The crude product was redissolved in EtOAc (100 ml) and stirred with Raney® nickel (12 ml of a 50% slurry in water) for 16 hours. The solution was filtered, separated, and the organic dried ($MgSO_4$), and palladium on carbon (750 mg, 10% Pd) was added followed by formic acid (5 ml). The reaction was stirred at ambient temperature for 1 h and filtered. The solvent was removed *in vacuo* and the crude reaction product purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford a yellow solid which could be recrystallised from MeOH to afford the *title compound* (0.56 g, 34%) as white needles, 81% e.e. by chiral HPLC. The maleate salt was crystallised from EtOAc affording white crystals of >96% e.e. by chiral HPLC, mp 214-216°C; δ_H (360 MHz, d_6-DMSO) 1.78-1.95 (1H, m, piperidine 5-H), 2.28-2.41 (1H, m, piperidine 5-H), 3.18-3.60 (5H, m, piperidine 2-H, 4-H and 6-H), 4.02-4.15 (1H, br, piperidine NH), 5.34 (1H, dtd, *J* 49, 8 and 4, piperidine 4-H), 6.01 (2H, s, maleic acid), 7.06 (1H, t, *J* 7, indole-H), 7.16 (1H, t, *J* 7, indole-H), 7.38-

7.43 (3H, m, 2 ArH and indole-H), 7.60-7.64 (2H, m, ArH), 7.94 (1H, d, *J* 8, indole-H), 8.6 (2H, br s, NH_2), 11.45 (1H, s, indole NH); *m/z* (ES^+) 313 (M^++H).

EXAMPLE 9

(3R,4R)-3-(4-Fluoro-1-methylpiperidin-3-yl)-2-phenyl-1*H*-indole

A solution of *(3R,4R)*-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole (100 mg, 0.34 mmol) in methanol (5 ml) was treated sequentially with glacial acetic acid (100 µl, 1.7 mmol), formaldehyde (60 µl of a 37 wt. % solution in water, 0.74 mmol) and sodium cyanoborohydride (50 mg, 0.80 mmol) and this mixture was stirred at ambient temperature for 3 hours. The reaction was then poured into a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The organics were washed with water, brine, dried over anhydrous sodium sulphate, filtered and pre-adsorbed onto silica. Purification on the same eluting with ethyl acetate/hexane/ triethylamine (50:49:1) gave the title compound as a colourless oil (100 mg, 95%). Oxalate salt, white powder, mp 240-242°C (from ethanol) (Found C, 66.03; H, 5.73; N, 6.82. $C_{22}H_{23}FN_2O_4$ requires C, 66.32; H, 5.82; N, 7.03); δ_H (360 MHz, d_6-DMSO) 1.84-2.02 (1H, m, piperidine 5-H), 2.26-2.38 (1H, m, piperidine 5-H), 2.71 (3H, s, NMe), 3.18-3.30 (1H, m, piperidine-H), 3.36-3.86 (4H, m, piperidine-H), 5.30 (1H, dtd, *J* 51, 10 and 5, C*H*F), 7.05 (1H, t, *J* 8, indole-H), 7.15 (1H, t, *J* 8, indole-H), 7.36-7.46 (2H, m, Ar-H), 7.48-7.66 (4H, m, Ar-H), 7.91 (1H, d, *J* 8, Ar-H), 11.42 (1H, s, indole NH); *m/z* (ES^+) 309 (M^+ + H).

EXAMPLE 10

(3R,4R*)*-6-Fluoro-3-(4-fluoropiperidin-3-yl)-2-(furan-3-yl)-1*H*-indole

A cooled (0°C) solution of potassium hydroxide (73 g, 1.3 mol) in methanol (900 ml) was treated with 6-fluoroindole (46 g, 0.34 mol) then 4-

piperidone monohydrate hydrochloride (138 g, 0.90 mol). The resulting suspension was magnetically stirred and heated under reflux for 60 hours. The reaction was cooled to ambient temperature, poured into water (8 l) and the resulting gummy solid stirred for 16 hours to furnish a fine suspension. The pale yellow solid was collected by filtration, washed with water and dried under vacuum to afford 6-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (86 g, >100% - contains water) which was used without further purification; δ_H (360 MHz, d_6-DMSO) 2.30-2.40 (2H, m, NCH_2CH_2), 2.92 (2H, t, *J* 6, NCH_2CH_2), 3.38-3.45 (2H, m, NCH_2CH), 6.15-6.20 (1H, m, NCH_2CH), 6.86 (1H, td, *J* 9 and 2, indole-H), 7.13 (1H, dd, *J* 9 and 2, indole-H), 7.35 (1H, d, *J* 2, indole 2-H), 7.78 (1H, dd, *J* 9 and 6, indole-H), 11.13 (1H, s, indole NH); *m/z* (ES^+) 217 (M^+ + H, 100%), 188 (M^+ - H_2C=NH, 20%).

A suspension of 6-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (86 g) in dichloromethane (1 l) was treated with triethylamine (142 ml, 1.02 mol) and then stirred and cooled to 0°C. Di-*tert*-butyl dicarbonate (163 g, 0.75 mol) was then added portionwise over 15 minutes followed by 4-dimethylaminopyridine (50 g, 0.41 mol) and the resulting solution stirred at ambient temperature for 90 minutes. The reaction was treated with *N,N*-dimethylethylenediamine (17 ml, 0.16 mol) and stirring continued at ambient temperature for 30 minutes. The majority of the solvent was removed on a rotary evaporator and the residue dissolved in ethyl acetate (2.5 l). This was washed with 0.01N hydrochloric acid (2 x 1.5 l), water, brine and then dried over anhydrous sodium sulphate. Filtration through a pad of Florisil® followed by evaporation to dryness gave 3-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester as a viscous yellow oil (110 g, 78% over 2 steps); δ_H (360 MHz, $CDCl_3$) 1.50 (9H, s, *tert*-butyl), 1.67 (9H, s, *tert*-butyl), 2.45-2.50 (2H, m, NCH_2CH_2), 3.67 (2H, t, *J* 6, NCH_2CH_2), 4.15-4.20 (2H, m, NCH_2CH), 6.10-6.15 (1H, m, NCH_2CH), 7.00 (1H, td, *J* 9 and

2, indole-H), 7.49 (1H, s, indole 2-H), 7.70 (1H, dd, *J* 9 and 5, indole-H), 7.85-7.90 (1H, m, indole-H).

A cooled (-10°C) flask containing solid (-)-diisopinocampheylborane (110 g, 0.38 mol) was treated with a solution of 3-(1-*tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (110 g, 0.26 mol) in anhydrous tetrahydrofuran (800 ml) and the resulting yellow suspension was stirred at ambient temperature for 90 hours to give a solution. The reaction was then cooled to -10°C and treated with 4N sodium hydroxide solution (500 ml) followed by hydrogen peroxide (300 ml of a 30 wt. % solution in water) and this mixture was stirred to ambient temperature over 24 hours. The majority of the tetrahydrofuran was removed on a rotary evaporator and the residue partitioned between ethyl acetate (2 l) and water (2 l). The organic phase was then washed with 0.1N hydrochloric acid (1.5 l), water (1.5 l), brine (1 l), dried over anhydrous sodium sulphate, filtered and evaporated to dryness to give *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-3-hydroxypiperidin-4-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester as a viscous liquid (151 g, >100%) which was taken forward to the next step without further purification. ^{1}H NMR analysis of the crude product showed isopinocampheol to be the major contaminant. For the purposes of identification a small sample was purified by chromatography on silica gel eluting with hexane on a gradient of ethyl acetate from 0-25% to afford a colourless, viscous oil; δ_H (360 MHz, $CDCl_3$) 1.50 (9H, s, *tert*-butyl), 1.67 (9H, s, *tert*-butyl), 1.80 (1H, d, *J* 3, OH), 1.80-1.85 (1H, m, piperidine 5-H), 1.90-1.95 (1H, m, piperidine 5-H), 2.64-2.74 (1H, m, piperidine-H), 2.76-2.84 (2H, m, piperidine-H), 3.75-3.84 (1H, m, piperidine-H), 4.15-4.26 (1H, m, piperidine-H), 4.35-4.45 (1H, m, C*H*OH), 6.99 (1H, td, *J* 9 and 2, indole-H), 7.44 (1H, s, indole 2-H), 7.53 (1H, dd, *J* 9 and 5, indole-H), 7.85-7.90 (1H, m, indole-H).

A solution of crude *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-3-hydroxypiperidin-4-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (151

g) in methanol (700 ml) was treated with solid sodium methoxide (70 g, 1.3 mol) and the resulting yellow/brown solution was stirred at 65°C for 16 hours. After cooling to ambient temperature a solution of glacial acetic acid (15 ml) in water (85 ml) was added, the methanol was removed on a rotary evaporator and the residue partitioned between ethyl acetate (2 l) and water (2 l). The organic phase was then washed with 0.01N hydrochloric acid (2 x 1.5 l), water (1.5 l), brine (1 l), dried over anhydrous sodium sulphate, filtered and evaporated to dryness to give a viscous oil. This oil was dissolved in the minimum volume of dichloromethane and then purified on a bed of silica (1.5 kg). Elution with hexane on a gradient of ethyl acetate (10-40%) gave *(3R*,4R*)*-4-(6-fluoro-1*H*-indol-3-yl)-3-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester as an oil (56 g, 63% over 2 steps, *ca.* 60% e.e. by HPLC). This oil was dissolved in ethyl acetate (100 ml) and heated to 65°C. Hexane was then added to this solution until just turbid and the heat source removed. After standing at ambient temperature for 16 hours the solid was removed by filtration and shown to be racemic. The filtrate was evaporated to dryness and the above procedure repeated giving a second crop of racemic solid (15 g combined mass). Concentration of the filtrate afforded a yellow foam (41 g, 88% e.e. by HPLC). This material was used in the subsequent steps; δ_H (360 MHz, $CDCl_3$) 1.50 (9H, s, *tert*-butyl), 1.86 (1H, d, *J* 2, OH), 1.82-1.90 (1H, m, piperidine 5-H), 1.90-1.98 (1H, m, piperidine 5-H), 2.64-2.74 (1H, m, piperidine-H), 2.78-2.86 (2H, m, piperidine-H), 3.68-3.78 (1H, m, piperidine-H), 4.16-4.26 (1H, m, piperidine-H), 4.38-4.46 (1H, m, C*H*OH), 6.90 (1H, td, *J* 9 and 2, indole-H), 7.02-7.08 (2H, m, indole 2-H and indole-H), 7.59 (1H, dd, *J* 9 and 5, indole-H), 8.22 (1H, br, indole NH).

A cooled (-78°C) solution of *(3R*,4R*)*-4-(6-fluoro-1*H*-indol-3-yl)-3-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (41 g, 0.12 mol) in ethyl acetate (750 ml) was treated over 5 minutes with diethylaminosulphur trifluoride (17.3 ml, 0.14 mol). Stirring at -78°C was continued for 1 hour before allowing the solution to warm to ambient

temperature over 3 hours. The reaction mixture was then poured into saturated aqueous sodium hydrogen carbonate (750 ml) and then diluted with ethyl acetate (750 ml). The organic phase was then washed with 0.1N hydrochloric acid (750 ml), water (750 ml), brine (750 ml), then dried over anhydrous sodium sulphate. This solution was filtered and evaporated to dryness to afford *(3R*,4R*)*-4-fluoro-3-(6-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic acid *tert*-butyl ester as an orange foam (43 g) which was contaminated with ca. 10% of an unknown impurity. Used in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, *tert*-butyl), 1.75-1.90 (1H, m, piperidine 5-H), 2.05-2.20 (1H, m, piperidine 5-H), 3.13-3.30 (3H, m, piperidine-H), 3.90-4.05 (1H, m, piperidine-H), 4.10-4.24 (1H, m, piperidine-H), 4.75-4.95 (1H, m, C*H*F), 6.96 (1H, td, *J* 9 and 2, indole-H), 7.00-7.13 (2H, m, indole 2-H and indole-H), 7.57 (1H, dd, *J* 9 and 5, indole-H), 8.09 (1H, br, indole NH).

A solution of crude *(3R*,4R*)*-4-fluoro-3-(6-fluoro-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (43 g) in dichloromethane (750 ml) was treated with triethylamine (34 ml, 0.24 mol) and then stirred and cooled to 0°C. Di-*tert*-butyl dicarbonate (31 g, 0.14 mol) was then added portionwise over 10 minutes followed by 4-dimethylaminopyridine (16.5 g, 0.14 mol) and the resulting solution stirred at ambient temperature for 16 hours. The reaction was treated with *N,N*-dimethylethylenediamine (5 ml) and stirring continued at ambient temperature for 30 minutes. The majority of the solvent was removed on a rotary evaporator and the residue dissolved in ethyl acetate (1 l). This was washed with 0.01N hydrochloric acid (2 x 1.5 l), water (1 l), brine (1 l) and then dried over anhydrous sodium sulphate. Filtration gave a brown solution which was treated with silica (250 g), evaporated to afford a powder and then this powder was applied to a bed of TLC grade silica (1.2 kg). Elution with hexane on a gradient of diethyl ether (10-30%) gave *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester as a pale yellow foam (36.5 g, 68% over 2 steps); δ_H (400 MHz,

$CDCl_3$) 1.47 (9H, s, *tert*-butyl), 1.66 (9H, s, *tert*-butyl), 1.74-1.86 (1H, m, piperidine 5-H), 2.10-2.22 (1H, m, piperidine 5-H), 3.04-3.20 (3H, m, piperidine-H), 4.00-4.11 (1H, m, piperidine-H), 4.15-4.31 (1H, m, piperidine-H), 4.82 (1H, dtd, *J* 48, 9 and 4, C*H*F), 7.00 (1H, td, *J* 9 and 2, indole-H), 7.47 (1H, s, indole 2-H), 7.51 (1H, dd, *J* 9 and 5, indole-H), 7.81-7.90 (1H, m, indole-H).

A cooled (-10°C) solution of 2,2,6,6-tetramethylpiperidine (506 µl, 3.0 mmol) in tetrahydrofuran (20 ml) was treated with *n*-butyllithium (1.9 ml of a 1.6M solution in hexane, 3.0 mmol). This mixture was stirred at -10°C for 5 minutes and then cooled to -78°C. To this solution was added a pre-cooled (-78°C) solution of *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (475 mg, 1.1 mmol) in tetrahydrofuran (7 ml) by means of a double-ended needle and stirring at -78°C was continued for 2 hours. Zinc chloride (4.4 ml of a 0.5M solution in diethyl ether, 2.2 mmol) was then added dropwise over 5 minutes to the reaction mixture and stirring at -78°C continued for 30 minutes before allowing the solution to warm to ambient temperature. 3-Bromofuran (200 µl, 2.2 mmol) followed by tetrakis(triphenylphosphine)-palladium(0) (65 mg) was then added and the reaction heated at 50°C for 16 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate (100 ml) and washed with a saturated solution of ammonium chloride, water, brine and the organics then dried over anhydrous sodium sulphate. After filtration the solution was pre-adsorbed onto silica and purified on the same. Elution with hexane on a gradient of diethyl ether (10-35%) gave *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoro-2-(furan-3-yl)indole-1-carboxylic acid *tert*-butyl ester as a white foam (372 mg, 68%); δ_H (360 MHz, $CDCl_3$) 1.42 (18H, s, *tert*-butyl), 1.60-1.74 (1H, m, piperidine 5-H), 2.08-2.22 (1H, m, piperidine 5-H), 2.76-3.22 (3H, m, piperidine-H), 3.96-4.14 (1H, m, piperidine-H), 4.18-4.32 (1H, m, piperidine-H), 4.84-5.12 (1H, m, C*H*F),

6.46 (1H, d, *J* 3, furan-H), 7.00 (1H, td, *J* 9 and 2, indole-H), 7.30-7.44 (3H, m, indole-H and furan-H), 7.96-8.04 (1H, m, indole-H).

A solution of *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoro-2-(furan-3-yl)indole-1-carboxylic acid *tert*-butyl ester (370 mg, 0.74 mmol) in methanol (10 ml) was treated with sodium methoxide (160 mg, 3 mmol) and the mixture heated at 60°C for 5 hours. The reaction was cooled to ambient temperature and the methanol removed on a rotary evaporator. The residue was suspended in ethyl acetate, washed with water, brine and dried over anhydrous sodium sulphate. Filtration and evaporation to dryness gave an oil. This oil was dissolved in 95% formic acid (5 ml) and stirred at ambient temperature for 16 hours. The reaction mixture was neutralised by the careful addition of a saturated solution of sodium hydrogen carbonate and then extracted with ethyl acetate. The organic extract was then washed with water, brine, dried over anhydrous sodium sulphate and filtered. The resulting solution was pre-adsorbed onto silica gel and purified on the same. Elution with dichloromethane/methanol/880 ammonia (95:4.5:0.5) gave the *title compound* as a cream-coloured solid (125 mg, 56%). Maleate salt, white powder, mp 211-213°C (from ethanol/ethyl acetate) (Found C, 60.43; H, 4.95; N, 6.60. $C_{21}H_{20}F_2N_2O_5$ requires C, 60.28; H, 4.82; N, 6.70); δ_H (360 MHz, d_6-DMSO) 1.92-2.00 (1H, m, piperidine 5-H), 2.12-2.24 (1H, m, piperidine 5-H), 3.31-3.64 (5H, m, piperidine-H), 5.20-5.42 (1H, m, C*H*F), 6.02 (2H, s, maleate), 6.86-6.96 (2H, m, furan-H and indole-H), 7.14 (1H, dd, *J* 10 and 2, indole-H), 7.84-7.92 (2H, m, indole-H and furan-H), 8.05 (1H, s, furan-H), 8.64 (1H, br, NH), 11.44 (1H, s, indole NH). *m/z* (ES^+) 303 ($M^+ + H$).

EXAMPLE 11

(3R,4R*)*-6-Fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid cyclohexylamide

A cooled (-10°C) solution of 2,2,6,6-tetramethylpiperidine (580 µl, 3.4 mmol) in tetrahydrofuran (30 ml) was treated with *n*-butyllithium (2.15 ml of a 1.6M solution in hexane, 3.4 mmol). This mixture was stirred at -10°C for 5 minutes and then cooled to -78°C. To this solution was added a pre-cooled (-78°C) solution of *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (750 mg, 1.7 mmol) in tetrahydrofuran (10 ml) by means of a double-ended needle and stirring at -78°C was continued for 2 hours. Cyclohexyl isocyanate (275 µl, 2.2 mmol) was added followed, after 10 seconds, by a 10% solution of glacial acetic acid in tetrahydrofuran (5 ml) and the reaction mixture stirred to ambient temperature. The reaction was diluted with ethyl acetate (100 ml) and washed with a saturated solution of sodium hydrogen carbonate, water, brine and the organics then dried over anhydrous sodium sulphate. After filtration the solution was pre-adsorbed onto silica and purified on the same. Elution with hexane on a gradient of diethyl ether (10-40%) gave recovered starting material (190 mg) followed by *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-2-cyclohexylcarbamoyl-6-fluoroindole-1-carboxylic acid *tert*-butyl ester as a white foam (656 mg, 91% based on recovered starting material); δ_H (360 MHz, $CDCl_3$) 1.12-1.32 (4H, m, cyclohexyl), 1.32-1.48 (2H, m, cyclohexyl), 1.45 (9H, s, *tert*-butyl), 1.63 (9H, s, *tert*-butyl), 1.66-1.82 (3H, m), 1.96-2.04 (1H, m), 2.04-2.12 (1H, m), 2.22-2.30 (1H, m), 2.80-2.92 (1H, m), 3.10-3.24 (1H, m), 3.26-3.38 (1H, m), 3.92-4.04 (1H, m), 4.10-4.22 (1H, m), 4.28-4.32 (1H, m), 5.04 (1H, dtd, *J* 53, 10 and 5, C*H*F), 6.00 (1H, br, amide NH), 7.00 (1H, td, *J* 9 and 2, indole-H), 7.51 (1H, dd, *J* 9 and 5, indole-H), 7.91 (1H, d, *J* 10, indole-H).

A solution of *(3R*,4R*)*-3-(1-*tert*-butoxycarbonyl-4-fluoropiperidin-3-yl)-2-cyclohexylcarbamoyl-6-fluoroindole-1-carboxylic acid *tert*-butyl ester (650 mg, 1.2 mmol) was dissolved in 95% formic acid (10 ml) and stirred at 45°C for 4 hours. After cooling to ambient temperature the reaction mixture was neutralised by the careful addition of a saturated solution of

sodium hydrogen carbonate and then extracted with ethyl acetate. The organic extract was then washed with water, brine, dried over anhydrous sodium sulphate and filtered. The resulting solution was pre-adsorbed onto silica gel and purified on the same. Elution with dichloromethane/methanol/0.880 ammonia (95:4.5:0.5) gave the *title compound* as a white foam (260 mg, 62%). Maleate salt, white powder, mp 220-222°C (from ethanol/ethyl acetate) (Found C, 60.45; H, 6.12; N, 8.67. $C_{24}H_{29}F_2N_3O_5$ requires C, 60.37; H, 6.12; N, 8.80); δ_H (360 MHz, d_6-DMSO) 1.12-1.30 (5H, m, cyclohexyl), 1.56-1.66 (1H, m, cyclohexyl), 1.68-1.80 (2H, m, cyclohexyl), 1.84-1.98 (3H, m), 2.30-2.40 (1H, m), 3.18-3.40 (2H, m), 3.40-3.48 (1H, m), 3.57 (1H, t, *J* 12), 3.69-3.82 (1H, m), 4.08-4.26 (1H, m), 5.38 (1H, dtd, *J* 48, 10 and 5, C*H*F), 6.02 (2H, s, maleate), 6.98 (1H, td, *J* 9 and 2, indole-H), 7.25 (1H, dd, *J* 10 and 2, indole-H), 7.86 (1H, dd, *J* 9 and 5, indole-H), 8.02 (1H, d, *J* 8, indole-H), 8.65 (1H, br, NH), 11.60 (1H, s, indole NH). *m/z* (ES^+) 362 ($M^+ + H$).

EXAMPLE 12

(3R,4R*)*-3-(2-Phenyl-1*H*-indol-3-yl)piperidin-4-ol

To a cooled (0°C) solution of *(3R*,4R*)*-4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (5.0 g, 11.7 mmol) in tetrahydrofuran (400 ml) was added triphenylphosphine (9.2 g, 35.1 mmol) followed by 4-nitrobenzoic acid (5.9 g, 35.3 mmol). Diethyl azodicarboxylate (5.5 ml, 34.9 mmol) was then added dropwise over 10 minutes and the resulting mixture was stirred to ambient temperature over 16 hours. The solvent was removed on a rotary evaporator and the residue suspended in water and extracted with diethyl ether (500 ml). The organics were washed with 1N sodium hydroxide (2 x 500 ml), 1N hydrochloric acid (500 ml), water, brine, dried over anhydrous sodium sulphate, filtered and pre-adsorbed onto silica. Purification of the same eluting with dichloromethane on a gradient of methanol (0-1.5%) gave 4-

(4-nitrobenzoyloxy)-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester as a yellow solid (6.21 g, 76%) (Found C, 70.87; H, 5.04; N, 7.24. $C_{34}H_{29}N_3O_6$ requires C, 70.94; H, 5.08; N, 7.30); δ_H (360 MHz, d_6-DMSO @ 340K) 1.61 (1H, qd, *J* 13 and 4, piperidine 5-H), 2.20-2.28 (1H, m, piperidine 5-H), 3.30-3.45 (2H, m, piperidine-H), 3.66 (1H, t, *J* 13, piperidine-H), 4.19 (2H, dd, *J* 14 and 4, piperidine-H), 5.08 (1H, d, *J* 13, PhC*H*$_2$O), 5.13 (1H, d, *J* 13, PhC*H*$_2$O), 5.78 (1H, td, *J* 11 and 5, piperidine 4-H), 6.99 (1H, t, J 8, indole-H), 7.05 (1H, t, *J* 8, indole-H), 7.27-7.56 (10H, m, ArH), 7.75 (2H, d, J 9, ArH *m*-NO_2), 7.88 (1H, d, *J* 8, ArH), 8.13 (2H, d, *J* 8, ArH *o*-NO_2), 11.03 (1H, s, NH).

A suspension of 4-(4-nitrobenzoyloxy)-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic acid benzyl ester (2.0 g, 3.5 mmol) in methanol (75 ml) was treated with potassium carbonate (5.0 g, 36 mmol) and this mixture was stirred at ambient temperature for 3 hours. The reaction was filtered, the filtrate evaporated to dryness, the residue suspended in water and extracted with ethyl acetate. The organic phase was then washed with water, brine, dried over anhydrous sodium sulphate, filtered and pre-adsorbed onto silica. Purification of the same eluting with hexane on a gradient of ethyl acetate (10-30%) gave 4-hydroxy-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester as a white foam (1.4 g, 95%) (Found C, 75.83; H, 6.22; N, 6.30. $C_{27}H_{26}N_2O_3$ requires C, 76.03; H, 6.14; N, 6.57); δ_H (360 MHz, $CDCl_3$) 1.50-1.63 (1H, m, piperidine 5-H), 1.82 (1H, d, *J* 2, OH), 2.08-2.14 (1H, m, piperidine 5-H), 2.94-3.12 (2H, m, piperidine-H), 3.38-3.51 (1H, m, piperidine-H), 4.22-4.46 (3H, m, piperidine-H), 5.11 (2H, s, PhC*H*$_2$O), 7.12 (1H, t, *J* 8, indole-H), 7.18-7.48 (10H, m, ArH), 7.50-7.60 (2H, m, ArH), 7.73 (1H, d, *J* 8, ArH), 8.23 (1H, s, NH).

A solution of 4-hydroxy-3-(2-phenyl-1*H*-indol-3-yl)piperidine-1-carboxylic acid benzyl ester (1.0 g, 2.3 mmol) in ethyl acetate (20 ml) and methanol (5 ml) was treated with 10% palladium on activated carbon (100 mg) and stirred under 1 atmosphere of hydrogen at ambient temperature

for 4 hours. The reaction mixture was filtered, evaporated to dryness and the residue triturated with chloroform/diethyl ether to afford the *title compound* as a white powder (583 mg, 85%); δ_H (360 MHz, d_6-DMSO) 1.49-1.59 (1H, m, piperidine 5-H), 1.96-2.03 (1H, m, piperidine 5-H), 3.00-3.45 (4H, m, piperidine-H), 4.19-4.28 (1H, m, piperidine-H), 4.76-4.86 (1H, m), 7.01-7.10 (1H, m, indole-H), 7.37-7.52 (4H, m, ArH), 7.70-7.88 (3H, m, ArH), 11.22 (1H, s, indole NH). *m/z* (ES^+) 293 ($M^+ + H$).

EXAMPLES 13 TO 51

Using the methods outlined above the following compounds were prepared:

Example 13: 2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole

Example 14: 6-fluoro-2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole

Example 15: 6-fluoro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 16: 6-fluoro-2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 17: 6-chloro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 18: 6-chloro-2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 19: 6-fluoro-2-(2-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 20: 6-chloro-2-(2-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 21: 6-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

Example 22: 5-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

Example 23: 6-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

Example 24: 5-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

Example 25: 7-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

Example 26: 7-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole

Example 27: 2-cyclohexyl-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 28: 2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-6-methyl-1*H*-indole

Example 29: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-methoxyphenyl)-1*H*-indole

Example 30: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-isopropoxy-phenyl)-1*H*-indole

Example 31: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(thien-2-yl)-1*H*-indole

Example 32: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(thien-3-yl)-1*H*-indole

Example 33: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(*m*-tolyl)-1*H*-indole

Example 34: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(*o*-tolyl)-1*H*-indole

Example 35: *(3R*,4R*)*-2-(benzo[1,3]dioxol-5-yl)-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole

Example 36: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyridin-3-yl)-1*H*-indole

Example 37: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyridin-4-yl)-1*H*-indole

Example 38: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyrimidin-5-yl)-1*H*-indole

Example 39: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(naphthalen-1-yl)-1*H*-indole

Example 40: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(naphthalen-2-yl)-1*H*-indole

Example 41: *(3R*,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]-benzonitrile

Example 42: *(3R*,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]-phenol

Example 43: *(3R*,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]-benzoic acid methyl ester

Example 44: *(3R*,4R*)*-*N*-{3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzyl}-*N*,*N*-dimethylamine

Example 45: *(3R*,4R*)*-{3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]phenyl}methanol

Example 46: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid phenylamide

Example 47: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid (4-chlorophenyl)amide

Example 48: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid methyl ester

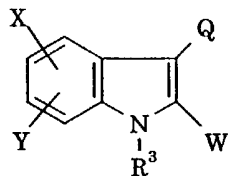
Example 49: *(3R*,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-indole

Example 50: *(3R*,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-ylcarbonylamino]benzoic acid ethyl ester

Example 51: *(3R*,4R*)*-3-(6-fluoro-2-phenyl-1*H*-indol-3-yl)piperidin-4-ol

CLAIMS:

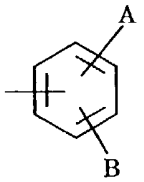
1. A compound of formula I, or a salt thereof:



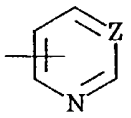
(I)

wherein

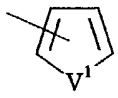
W represents cyclohexyl, $-CO_2R^4$, $-CONHR^5$, or a group of formula (Wa), (Wb), (Wc) or (Wd):



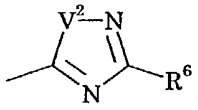
(Wa)



(Wb)



(Wc)



(Wd)

in which

Z represents CH or N;

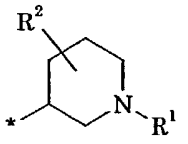
V^1 represents oxygen or sulphur;

V^2 represents oxygen or sulphur;

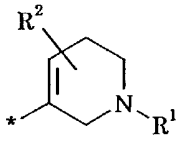
A and B independently represent hydrogen, hydroxy, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, hydroxymethyl or di(C_{1-6})alkylaminomethyl; or A and B, when situated on adjacent carbon atoms, together represent $-OCH_2O-$ or -CH=CH-CH=CH-;

X and Y independently represent hydrogen, halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy or phenyl;

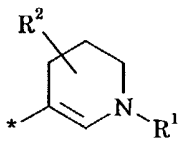
Q represents a group of formula (Qa), (Qb) or (Qc):



(Qa)



(Qb)



(Qc)

in which the asterisk denotes the point of attachment to the 3-position of the indole nucleus;

R^1 represents hydrogen, C_{1-6} alkyl, or an optionally substituted aryl(C_{1-6})alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl group;

R^2 represents hydrogen, hydroxy, halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

R^3 represents hydrogen or C_{1-6} alkyl;

R^4 represents C_{1-6} alkyl;

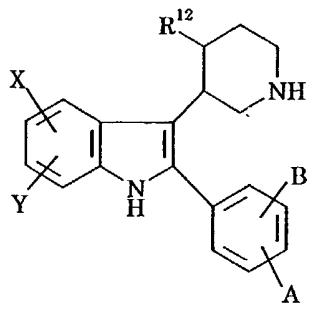
R^5 represents cyclohexyl, or a group of formula (Wa) as defined above; and

R^6 represents C_{1-6} alkyl, cyclohexyl, or a group of formula (Wa) as defined above.

2. A compound as claimed in claim 1 wherein W represents a group of formula (Wa) as defined in claim 1.

3. A compound as claimed in claim 1 or claim 2 wherein Q represents a group of formula (Qa) as defined in claim 1.

4. A compound as claimed in any one of the preceding claims represented by formula II, and salts thereof:



(II)

wherein

A, B, X and Y are as defined in claim 1; and

R^{12} represents hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy.

5. A compound selected from:

3-(1-benzylpiperidin-3-yl)-2-phenyl-1*H*-indole;

3-(piperidin-3-yl)-2-phenyl-1*H*-indole;

3-[1-(2-phenylethyl)piperidin-3-yl]-2-phenyl-1*H*-indole;

3-(1-methylpiperidin-3-yl)-2-phenyl-1*H*-indole;

1-{2-[3-(2-phenyl-1*H*-indol-3-yl)piperidin-1-yl]ethyl}imidazolidin-2-one;

(3RS,4RS)-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

(+)-(3R,4R*)*-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

(+)-(3R,4R*)*-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

and salts thereof.

6. A compound selected from:

(3R,4R)-3-(4-fluoro-1-methylpiperidin-3-yl)-2-phenyl-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(furan-3-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid cyclohexylamide;

(3R,4R*)*-3-(2-phenyl-1*H*-indol-3-yl)piperidin-4-ol;

2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole;

6-fluoro-2-(4-fluorophenyl)-3-(piperidin-3-yl)-1*H*-indole;

6-fluoro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-fluoro-2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-chloro-2-(4-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-chloro-2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-fluoro-2-(2-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-chloro-2-(2-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

6-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

5-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

6-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

5-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

7-chloro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

7-fluoro-3-(4-fluoropiperidin-3-yl)-2-phenyl-1*H*-indole;

2-cyclohexyl-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

2-(3-fluorophenyl)-3-(4-fluoropiperidin-3-yl)-6-methyl-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-methoxyphenyl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-isopropoxyphenyl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(thien-2-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(thien-3-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(*m*-tolyl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(*o*-tolyl)-1*H*-indole;

(3R,4R*)*-2-(benzo[1,3]dioxol-5-yl)-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyridin-3-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyridin-4-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(pyrimidin-5-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(naphthalen-1-yl)-1*H*-indole;

(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(naphthalen-2-yl)-1*H*-indole;

(3R,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzonitrile;

(3R,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]phenol;

(3R,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzoic acid methyl ester;
(3R,4R*)*-*N*-{3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]benzyl}-*N,N*-dimethylamine;
(3R,4R*)*-{3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-yl]phenyl}methanol;
(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid phenylamide;
(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid (4-chlorophenyl)amide;
(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indole-2-carboxylic acid methyl ester;
(3R,4R*)*-6-fluoro-3-(4-fluoropiperidin-3-yl)-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-indole;
(3R,4R*)*-3-[6-fluoro-3-(4-fluoropiperidin-3-yl)-1*H*-indol-2-ylcarbonylamino]benzoic acid ethyl ester;
(3R,4R*)*-3-(6-fluoro-2-phenyl-1*H*-indol-3-yl)piperidin-4-ol;
and salts thereof.

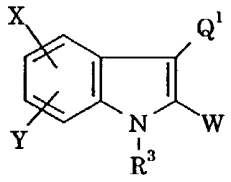
7. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

8. A composition as claimed in claim 7 further comprising another anti-schizophrenic medicament.

9. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

10. A process for the preparation of a compound as claimed in claim 1, which comprises:

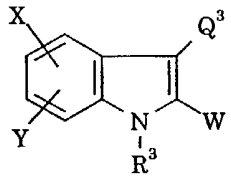
(A) attachment of the R^1 moiety to a compound of formula III:



(III)

wherein W, X, Y and R^3 are as defined in claim 1, and Q^1 represents a group of formula (Qa), (Qb) or (Qc) as defined in claim 1 in which R^1 is hydrogen; or

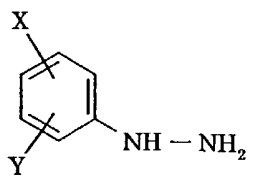
(B) reducing a compound of formula V:



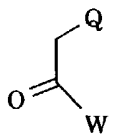
(V)

wherein W, X, Y and R^3 are as defined in claim 1, and Q^3 represents a group of formula (Qb) or (Qc) as defined in claim 1; or

(C) reacting a compound of formula VIII or an acid addition salt thereof with a compound of formula IX:



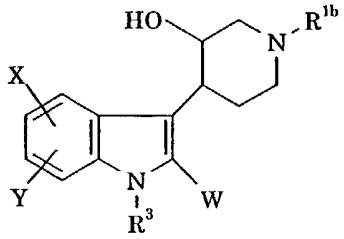
(VIII)



(IX)

wherein W, X, Y and Q are as defined in claim 1; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3; or

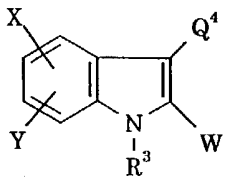
(D) treating a compound of formula X:



(X)

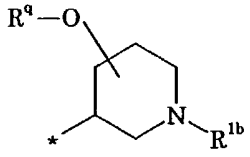
wherein W, X, Y and R^3 are as defined in claim 1, and R^{1b} represents an amino-protecting group or corresponds to the moiety R^1 as defined in claim 1; with diethylaminosulphur trifluoride; followed, where necessary, by removal of the amino-protecting group; or

(E) removing the hydroxy-protecting group from a compound of formula XII:

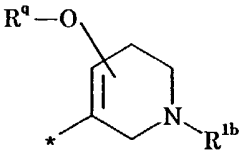


(XII)

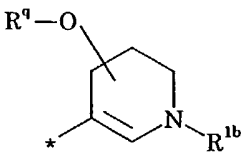
wherein W, X, Y and R^3 are as defined in claim 1, and Q^4 represents a group of formula (Qf), (Qg) or (Qh):



(Qf)



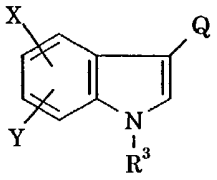
(Qg)



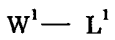
(Qh)

in which the asterisk denotes the point of attachment to the 3-position of the indole nucleus, R^{1b} is as defined above, and R^q represents a hydroxy-protecting group; followed, where necessary, by removal of the amino-protecting group; or

(F) reacting a compound of formula XIV with a compound of formula XV:



(XIV)



(XV)

wherein X, Y, Q and R^3 are as defined in claim 1, W^1 represents cyclohexyl or a group of formula (Wa), (Wb), (Wc) or (Wd) as defined in claim 1, and L^1 represents a suitable leaving group; in the presence of a transition metal catalyst; or

(G) reacting a compound of formula XIV as defined above with a compound of formula R^5-N=C=O wherein R^5 is as defined in claim 1; in the presence of a transition metal catalyst; with subsequent acidification; and

(H) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

11. A method for the treatment and/or prevention of psychotic disorders which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

In .tional Application No
PCT/GB 99/00802

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/445 C07D401/14 C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 465 398 A (H. LUNBECK A/S) 8 January 1992 see page 2 - page 3	1,9
A	EP 0 747 379 A (ADIR ET COMPAGNIE) 11 December 1996 see page 13; claim 1	1,9
A	US 5 112 838 A (JENS PERREGAARD ET AL.) 12 May 1992 see column 2, line 46 - column 3, line 49	1,9
P,X	WO 99 11641 A (MERCK SHARP & DOHME LTD.) 11 March 1999 see page 3, line 28 - page 4	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1999	24/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

..ernational application No.
PCT/GB 99/00802

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/GB 99/00802

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 465398	A	08-01-1992	AT	115576	T	15-12-1994
			AU	644186	B	02-12-1993
			AU	8014491	A	02-01-1992
			CA	2045955	A	03-01-1992
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